REMARKS

Applicants have carefully studied the Office Action mailed on April 25, 2003, which issued in connection with the above-identified application. The present response is intended to be fully responsive to all points raised by the Examiner. Favorable reconsideration and an early action on the merits is respectfully requested.

Claims 1-35 are pending and at issue in this application.

In the Action, the Examiner required restriction to one of the following Groups of claims under 35 U.S.C. § 372, 37 C.F.R. § 1.499 and PCT Rule 13.1:

Group I: claim(s) 1 in part[1], 2, 6 in part, 9-12, 16, 19-23, allegedly drawn to a heterodimeric receptor, wherein the first receptor is a delta opioid receptor and the second receptor is an opioid receptor, including kappa and mu.

Group II: claim(s) 1 in part, 3, 6 in part, 9-11, 13, 16, 19-23, allegedly drawn to a heterodimeric receptor, wherein the first receptor is a delta opioid receptor and the second receptor is a dopamine receptor.

Group III: claim(s) 1 in part, 4, 6 in part, 9-11, 14, 16, 19-23, allegedly drawn to a heterodimeric receptor, wherein the first receptor is a delta opioid receptor and the second receptor is an adrenergic receptor.

Group IV: claim(s) 1 in part, 5, 9-11, 15, 16, 19-23, allegedly drawn to a heterodimeric receptor, wherein the first receptor is a delta opioid receptor and the second receptor is a chemokine receptor.

[1] Applicants respectfully request that the Examiner clarifies the meaning of the term "in part." Specifically, it is not clear to the applicants why this term is used with respect to some claims listed in a few different groups but not the others.

Group V: claim(s) 1 in part, 2, 7 in part, 9-12, 17, 19-23, allegedly drawn to a heterodimeric receptor, wherein the first receptor is a kappa opioid receptor and the second receptor is a delta opioid receptor.

Group VI: claim(s) 1 in part, 3, 7 in part, 9-11, 13, 17, 19-23, allegedly drawn to a heterodimeric receptor, wherein the first receptor is a kappa opioid receptor and the second receptor is a dopamine receptor.

Group VII: claim(s) 1 in part, 4,7 in part, 9-11, 14, 17, 19-23, allegedly drawn to a heterodimeric receptor, wherein the first receptor is a kappa opioid receptor and the second receptor is an adrenergic receptor.

Group VIII: claim(s) 1 in part, 5, 7 in part, 9-11, 15, 17, 19-23, allegedly drawn to a heterodimeric receptor, wherein the first receptor is a kappa opioid receptor and the second receptor is a chemokine receptor.

Group IX: claim(s) 1 in part, 2, 8 in part, 9-12, 18, 19-23, allegedly drawn to a heterodimeric receptor, wherein the first receptor is a mu opioid receptor and the second receptor is a delta opioid receptor.

Group X: claim(s) 1 in part, 4, 8 in part, 9-11, 14, 18, 19-23, allegedly drawn to a heterodimeric receptor, wherein the first receptor is a mu opioid receptor and the second receptor is an adrenergic receptor.

Group XI: claims 24-28, drawn to a bispecific compound.

Group XII: claim 29 in part and 33 in part, drawn to a pharmaceutical composition comprising a delta opioid receptor ligand and a kappa or mu opioid receptor ligand and a method of treating a disease.

Group XIII: claim 29 in part and 33 in part, drawn to a pharmaceutical composition comprising a delta opioid receptor ligand and a dopamine receptor ligand and a method of treating a disease.

Group XIV: claim 29 in part and 33 in part, drawn to a pharmaceutical composition comprising a delta opioid receptor ligand and a adrenergic receptor ligand and a method of treating a disease.

Group XV: claim 30 in part and 34 in part, drawn to a pharmaceutical composition comprising a kappa opioid receptor ligand and a delta opioid receptor ligand and a method of treating a disease.

Group XVI: claim 30 in part and 34 in part, drawn to a pharmaceutical composition comprising a kappa opioid receptor ligand and a dopamine receptor ligand and a method of treating a disease.

Group XVII: claim 30 in part and 34 in part, drawn to a pharmaceutical composition comprising a kappa opioid receptor ligand and an adrenergic receptor ligand and a method of treating a disease.

Group XVIII: claim 30 in part and 34 in part, drawn to a pharmaceutical composition comprising a kappa opioid receptor ligand and a chemokine receptor ligand and a method of treating a disease.

Group XIX: claim 31 in part and 35 in part, drawn to a pharmaceutical composition comprising a mu opioid receptor ligand and a delta opioid receptor ligand and a method of treating a disease.

Group XX: claim 31 in part and 35 in part, drawn to a pharmaceutical composition comprising a mu opioid receptor ligand and an adrenergic receptor ligand and a method of treating a disease.

Group XXI: drawn to a method of treating a disease using the compound of claim 24.[2]

In the Action, the Examiner contends that claims of each of the designated groups do not relate to a single inventive concept under PCT Rule 13.1, because, under PCT Rule 13.2, they lack the same or corresponding special technical feature. The Examiner argues that the inventions are distinct, because allegedly the products of Groups I-XXI are structurally and functionally distinct and the special technical feature of each group does not correspond to the special technical feature of any other group, *i.e.*, (i) the special technical feature of Groups I-X is the independent and distinct heterodimeric receptors; (ii) the special technical feature of Group XI is a bispecific ligand; (iii) the special technical feature of Groups XII-XXI is pharmaceutical compositions comprising ligands for each of the independent and distinct receptors as well as methods of treating a disease.

In order to be fully responsive to the Requirement for Restriction, applicants hereby elect, with traverse, to prosecute the claims of Group I (claims 1, 2, 6, 9-12, 16, and 19-23).

[2] Applicants respectfully note that, in the Action, claim 32 has not been placed in any group. Applicants have assumed that this claim is in Group XXI, which is missing the corresponding claim number. The Examiner is respectfully asked to confirm whether this understanding is correct. If it is correct, it is further unclear to the applicants why, in contrast to Groups XII-XX, which encompass both composition and treatment claims, claim 32 directed to a method of treating a disease by administering the compound of claim 24 has been grouped separately from claim 24 (Group XI).

In the Action, the scope of the claims of Group I is limited by the Examiner as drawn to a heterodimeric receptor, wherein the first receptor is a delta opioid receptor and the second receptor is an opioid receptor, including kappa and mu. Applicants respectfully note that, in contrast to the Examiner's assertion, only claims 1, 2, 6, and 9-10 are directed to heterodimeric receptors, while claims 11-12 are directed to recombinant host cells that expresses said heterodimeric receptors and claims 19-23 are directed to a method of screening for a compound that modulates a property of a heterodimeric receptor, wherein both receptor subunits are expressed endogenously in the same type of cell, which method comprises observing a change in a property of the heterodimeric receptor contacted with a candidate compound.

Although applicants are making the above election to be fully responsive to the Requirement for Restriction, applicants respectfully traverse the Requirement and reserve the right to petition therefrom under 37 C.F.R. § 1.144. In particular, applicants respectfully request reconsideration and modification of the Restriction Requirement to allow prosecution of the claims of Groups I-X in the same application, for the reasons provided as follows.

The present application is a U.S. national stage application based upon International Application No. PCT/US00/16559. As specified in 35 U.S.C. § 372. governing requirements and procedure for U.S. national stage, "the Director may cause the question of unity of invention to be reexamined under section 121 of this title." Under 35 U.S.C. § 121, "two or more independent and distinct inventions . . . in one application may . . . be restricted to one of the inventions". Inventions are "independent" if there is no distinct relationship between the two or more subjects disclosed" (MPEP 802.01). The term "distinct" means that "two or more subjects as disclosed are related . . . but are capable of separate manufacture, use or sale as claimed, AND ARE PATENTABLE (novel and unobvious) OVER EACH OTHER" (MPEP

802.01, July 1988) (emphasis in original). However, even with patentably distinct inventions, restriction is not required unless one of the following reasons appear (MPEP 808.02):

1. Separate classification;

2. Separate status in the art; or,

3. Different field of the search.

Moreover, according to Patent Office examining procedures, "[i]f the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to distinct or independent inventions" (MPEP 803) (emphasis added).

Applicants respectfully submit that the claims of Groups I-X contain multiple unifying features and the search of the features of these claims would be necessarily co-extensive.

Thus, applicants respectfully submit that the Examiner has segregated claims 2-10 directed to heterodimeric receptors into ten different groups overlooking the fact that all of these claims depend from claim 1, which is a genus claim. The same was done to claims 12-18, directed to recombinant host cells (which all depend from claim 11) and claims 20-23 directed to a method of screening for modulatory compounds (which all depend from claim 19).

Applicants further note that, as recited in claims 1-10 and disclosed, *e.g.*, at p. 5, ll. 19-26 of the specification, the present invention encompasses any isolated heterodimeric receptor comprising an opioid receptor subunit and another, different G-protein coupled receptor subunit, which is either a different opioid receptor protein or a non-opioid receptor, such as dopamine receptor, adrenergic receptor, or chemokine receptor. Non-limiting examples of such heterodimeric receptors are provided, *e.g.*, at p. 11, ll. 16-21 of the specification and include

opioid receptor kappa and the D2 dopamine receptor; opioid receptor delta and D2; opioid receptors mu and delta; opioid receptor mu and α2-adrenergic receptor; opioid receptor delta and α2-adrenergic receptor; opioid receptor delta and β2-adrenergic receptor; opioid receptors kappa and delta; opioid receptor kappa and β2-adrenergic receptor; opioid receptor kappa and ORL1 (nociceptin) receptor; opioid receptor delta and ORL1 (nociceptin) receptor; and opioid receptor kappa and CCR5 and CXCR4 chemokine receptors. Accordingly, the specific heterodimeric receptors recited in dependent claims 2-10, which have been identified by the Examiner as allegedly different "inventions" (Groups I-X), are really just different species of the same genus encompassed by the independent claim 1. Moreover, some of the different heterodimeric receptors recited in claims 2-10 comprise identical subunits, which would necessarily result in overlapping searches.

In light of the foregoing arguments, it can be concluded that the claims of provisionally elected Group I contain multiple unifying features with the claims of Groups II-X. Hence, it is believed that a single search of the features of the claims of Group I would necessarily and inescapably require a search of the subject matter of the claims of Groups II-X. The claims of Groups I-X represent a web of knowledge and continuity of effort that merits examination in a single application. The search and examination of each group is necessarily co-extensive, and in any event would involve such interrelated art that the search and examination of the entire application can be made without undue burden on the Examiner. Accordingly, applicants respectfully request that the Examiner modifies the Requirement to allow prosecution of Groups I-X together in the same application.

CONCLUSION

Applicants request entry of the foregoing remarks in the file history of this application. In view of the above arguments, reconsideration and modification of the Requirement for Restriction is respectfully requested, and an early action on the merits is courteously solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned agent at (212) 527-7634. The Examiner is hereby authorized to charge any additional fees associated with this response to our Deposit Account No. 04-0100.

Respectfully submitted,

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APPENDIX

PENDING CLAIMS: June 6, 2003
(Application Serial No.: 10/018,200 Filed: January 23, 2002)

1. An isolated heterodimeric receptor, which receptor comprises an opioid receptor subunit and a second G-protein coupled receptor (GPCR) subunit, wherein both receptor subunits are expressed endogenously in the same type of cell.

2. The heterodimeric receptor of claim 1, wherein the second receptor is an opioid receptor that is distinct from the first opioid receptor.

3. The heterodimeric receptor of claim 1, wherein the second receptor is a dopamine receptor.

4. The heterodimeric receptor of claim 1, wherein the second receptor is an adrenergic receptor.

5. The heterodimeric receptor of claim 1, wherein the second receptor is a chemokine receptor.

6. The heterodimeric receptor of claim 1, wherein the opioid receptor is a delta opioid receptor and the second receptor is selected from the group consisting of kappa opioid receptor, mu opioid receptor, D2 dopamine receptor, and β2-adrenergic receptor.

7. The heterodimeric receptor of claim 1, wherein the opioid receptor is a kappa opioid receptor and the second receptor is selected from the group consisting of delta opioid receptor, D2 dopamine receptor, α2-adrenergic receptor, β2-adrenergic receptor, CCR5, and CXCR4.

8. The heterodimeric receptor of claim 1, wherein the opioid receptor is a mu opioid receptor and the second receptor is selected from the group consisting of delta opioid receptor and α2-adrenergic receptor.

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9. The heterodimeric receptor of claim 1, wherein the opioid receptor is a fusion protein comprising a sequence of a functional opioid receptor protein and a tag sequence.

10. The heterodimeric receptor of claim 1, wherein the second receptor is a fusion protein comprising a sequence of a functional second receptor protein and a tag sequence.

11. A recombinant host cell that expresses a functional heterodimeric receptor, which receptor comprises an opioid receptor subunit expressed from an expression vector introduced into the host cell, and a second G-protein coupled receptor (GPCR) subunit expressed from an expression vector introduced into the host cell, wherein both receptor subunits are expressed endogenously in the same type of cell.

12. The host cell of claim 11, wherein the second receptor is a different opioid receptor or a covalently associated opioid receptor.

13. The host cell of claim 11, wherein the second receptor is a dopamine receptor.

14. The host cell of claim 11, wherein the second receptor is an adrenergic receptor.

15. The host cell of claim 11, wherein the second receptor is a chemokine receptor.

16. The host cell of claim 11, wherein the opioid receptor is a delta opioid receptor and the second receptor is selected from the group consisting of kappa opioid receptor, mu opioid receptor, D2 dopamine receptor, and β2-adrenergic receptor.

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17. The host cell of claim 11, wherein the opioid receptor is a kappa opioid receptor and the second receptor is selected from the group consisting of delta opioid receptor, D2 dopamine receptor, α2-adrenergic receptor, β2-adrenergic receptor, CCR5, and CXCR4.

18. The host cell of claim 11, wherein the opioid receptor is a mu opioid receptor and the second receptor is selected from the group consisting of delta opioid receptor and α2-adrenergic receptor.

19. A method of screening for a compound that modulates a property of a heterodimeric receptor, which receptor comprises an opioid receptor subunit and a second G-protein coupled receptor (GPCR) subunit, wherein both receptor subunits are expressed endogenously in the same type of cell, which method comprises observing a change in a property of the heterodimeric receptor contacted with a candidate compound.

20. The method according to claim 19, wherein the heterodimeric receptor property is trafficking of the heterodimeric receptor.

21. The method according to claim 19, wherein the heterodimeric receptor property is binding affinity for a ligand.

22. The method according to claim 19, wherein the heterodimeric receptor property is activation of a signal transduction pathway.

23. The method according to claim 22, wherein the signal transduction pathway is selected from the group consisting of cAMP production and MAPK phosphorylation.

24. A bispecific, bivalent compound comprising an opioid receptor ligand bound to a second G-protein coupled receptor ligand, wherein the second receptor is expressed endogenously in a type of cell that endogenously expresses the opioid receptor.

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25. The compound of claim 24, wherein both ligands are agonists.

26. The compound of claim 24, wherein both ligands are antagonists.

27. The compound of claim 24, wherein both ligands are kappa receptor ligands.

28. The compound of claim 24, wherein the opioid receptor ligand is a kappa receptor agonist and the second receptor ligand is a delta receptor agonist.

29. A pharmaceutical composition comprising synergistically effective amounts of a ligand of a delta opioid receptor and a ligand of a second receptor selected from the group consisting of kappa opioid receptor, mu opioid receptor, D2 dopamine receptor, and β2-adrenergic receptor.

30. A pharmaceutical composition comprising synergistically effective amounts of a ligand of a kappa opioid receptor and a ligand of a second receptor selected from the group consisting of delta opioid receptor, D2 dopamine receptor, α2-adrenergic receptor, β2-adrenergic receptor, CCR5, and CXCR4.

31. A pharmaceutical composition comprising synergistically effective amounts of a ligand of a mu opioid receptor and a ligand of a second receptor selected from the group consisting of delta opioid receptor and α2-adrenergic receptor.

32. A method of treating a disease or disorder selected from the group consisting of chronic pain, drug abuse, schizophrenia, depression, central reward pathway, HIV infection, cardiovascular disease, and hypertension, which method comprises administering a therapeutically effective dose of a compound of claim 24.

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33. A method of treating a disease or disorder selected from the group consisting of chronic pain, drug abuse, schizophrenia, depression, central reward pathway, HIV infection, cardiovascular disease, and hypertension, which method comprises administering a therapeutically effective dose of a pharmaceutical composition of claim 29.

34. A method of treating a disease or disorder selected from the group consisting of chronic pain, drug abuse, schizophrenia, depression, central reward pathway, HIV infection, cardiovascular disease, and hypertension, which method comprises administering a therapeutically effective dose of a pharmaceutical composition of claim 30.

35. A method of treating a disease or disorder selected from the group consisting of chronic pain, drug abuse, schizophrenia, depression, central reward pathway, HIV infection, cardiovascular disease, and hypertension, which method comprises administering a therapeutically effective dose of a pharmaceutical composition of claim 31.